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Randomized Trial-PrEscription of intraDialytic exercise to improve quAlity of Life in Patients Receiving Hemodialysis

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Randomized Trial - PrEscription of intraDialytic exercise to improve quAlity of Life (PEDAL) in patients receiving hemodialysis

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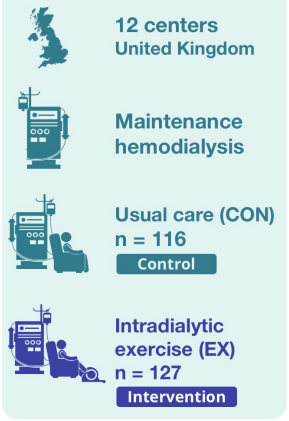

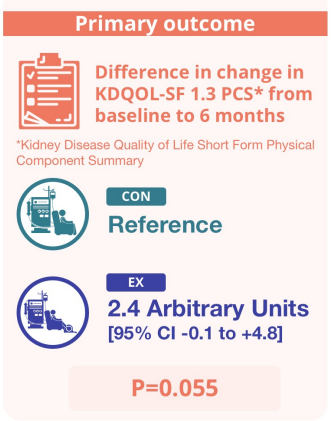

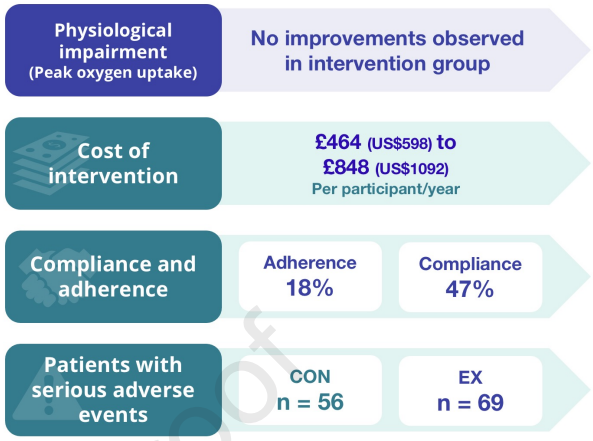

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Conclusion In the PEDAL trial, a six-month intradialytic aerobic exercise program was not clinically beneficial in improving HRQoL as delivered to this cohort of deconditioned patients on hemodialysis.

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Randomized Trial - PrEscription of intraDialytic exercise to improve quAlity of Life (PEDAL) in patients receiving hemodialysis

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ABSTRACT

Introduction: Whether clinically implementable exercise interventions in people receiving hemodialysis therapy improves health-related quality of life (HRQoL) remains unknown. The PEDAL study evaluated the clinical benefit and cost effectiveness of a six-month intradialytic exercise program.

Methods: In a multicenter, single-blinded, randomized controlled trial, people receiving hemodialysis were randomly assigned to i)intradialytic exercise training (EX), ii)usual care (CON). Primary outcome was change in Kidney Disease Quality of Life Short Form Physical Component Summary (KDQOL-SF 1.3 PCS) from baseline to six-months. Cost effectiveness was determined using health economic analysis; physiological impairment assessed by peak oxygen uptake; and harms were recorded.

Results: We randomized 379 participants; 335 patients completed baseline assessments and 243 patients (EX n=127; CON n=116) completed six-month assessments. Mean difference in change PCS from baseline to six months between EX and CON was 2.4 {95% confidence interval: -0.1 to 4.8} Arbitrary Units (p=0.055); no improvements were observed in peak oxygen uptake or secondary outcome measures. Participants in the intervention group had poor compliance (47%) and poor adherence (18%) to the exercise prescription. Cost of delivering intervention ranged from US$598 to US$1,092 per participant/year. Number participants with harms were similar between EX (n = 69) and CON (n = 56). A primary limitation was lack of an attention control group. Also, many patients withdrew from the study or were too unwell to complete all physiological outcome assessments.

Conclusions: A six-month intradialytic aerobic exercise program was not clinically beneficial in improving HRQoL as delivered to this cohort of deconditioned patients on hemodialysis.

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INTRODUCTION

Improved hemodialysis (HD) techniques and management of co-existing disease has improved the average life expectancy of patients receiving HD therapy globally, but disability and associated symtpoms remain highly prevalent accounting for more life years lost to disability (1). In the United Kingdom (UK), 48% of the HD population report severe functional dependencies (2), which impact on health-related quality of life (HRQoL) (3). Components of HRQoL, particularly the domain of physical functioning, stands out as the strongest predictor of survival, hospitalizations and morbidity (4). Knight et al (5) and Lowrie et al (6) report multiple symptoms that impact upon the physical component of HRQoL (7). Moreover, higher levels of physical activity are associated with better scores in HRQoL measures, physical functioning, depression and burden of kidney disease symptoms (8).

The physical component of HRQoL therefore, may be targeted with interventions to enhance physical activity. In patients receiving HD therapy, systematic reviews indicate that a range of exercise training interventions improve physical function and alleviate disability symptoms (9-22). Of particular interest are studies that have investigated intradialytic exercise, as the environment of unit-based HD provides a platform for longer-term sustainable implementation of exercise rehabilitation programs (23). The pre-existing need for patients to attend for standard thrice weekly, 4 hour-long HD sessions, provides an opportunity to deliver a structured and supervised rehabilitation program with reduced patient burden in terms of time, effort and travel costs (24, 25). Thus, physical activity behaviors could be promoted using an implementation model that integrates physical activity into the main health care system for patients receiving HD therapy.

However, very few dialysis units have chosen to implement this physical rehabilitation option in the UK. A barrier to implementation has been a lack of high-quality,

adequately powered randomized controlled trials (RCTs) of intradialytic exercise with patient reported outcomes (HRQoL), health economics (cost effectiveness) and harms (Serious Adverse Events) as the primary outcomes. Thus, the balance of benefits to costs and harms has been impossible to evaluate. Consequently, the PEDAL trial was commissioned by the National Institute for Health Research to evaluate whether intradialytic exercise was able to improve HRQoL in patients receiving HD therapy. The primary objective was to determine, in stage 5 chronic kidney disease patients receiving maintenance HD, whether usual care augmented by intradialytic exercise training for a period of six months improved The Kidney Disease Quality of Life Short Form Physical Component Summary (KDQOL-SF 1.3 PCS).

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METHODS

Trial design and oversight

We conducted this pragmatic prospective randomized controlled trial in 5 regions (London, Scotland, Wales, North West England and Midlands), across a total of 12 hemodialysis units, in the UK. The trial recruited prevalent patients with stage 5D CKD, receiving HD therapy. Briefly, the intervention consisted of using a modified cycle ergometer, to perform aerobic exercise in a semi-recumbent position, three times per week during the first two hours of HD. Twice per week, after the aerobic cycling exercise, participants completed lower extremity muscular conditioning exercises. These included 3 sets of 10-15 repetitions of dynamic resistance exercises for all major muscle groups. All exercises were performed against body weight before progression with ankle weights and TheraBands. The exercise program was delivered and supervised by physiotherapy assistants.

London Fulham Research Ethics Committee approved the protocol (14/LO/1851) and all the participants provided written informed consent. The study was registered prospectively (ISRCTN N83508514). The trial protocol and details on inclusion/exclusion criteria, randomization procedure and exercise intervention and prescription have been described elsewhere (26). The CONSORT Extension for Patient Report Outcomes also suggested reporting all the multi-item scales from the Kidney Disease Quality of Life Short Form instrument.

Primary Outcome

The primary outcome for this study was the change in Kidney Disease Quality of Life Short Form Physical Component Summary (KDQOL-SF 1.3 PCS) from baseline to six months (27). The KDQOL-SF 1.3 instrument was chosen because of its validity in patients with CKD and inclusion of a generic core that has been widely used in CKD and other populations. The

KDQOL-SF 1.3 is a disease-specific quality of life measure that includes 43 kidney disease targeted items and 36 items that provide a generic core and an overall health rating item. The questionnaire was completed by patients using pen and paper, with queries answered by research officers blinded to treatment allocation. Scoring followed currently recommended methods (28). Thus, the PCS score can be interpreted as follows: a score above or below 50 is above or below the average, respectively, in the US general population, whilst a one-point difference in score is one-tenth of a standard deviation. Analysis of within trial change in the KDQOL-SF 1.3 PCS score from baseline, adjusted for baseline levels and randomisation minimisation variables, suggested that the study had 80% power to detect a 4-point difference with only 87 participants per group (with complete data at baseline and 6-month follow-up).

Secondary outcomes

Health-related quality of life, cost effectiveness and harms

From the KDQOL-SF 1.3, the multi-item scale of Energy/Fatigue and the kidney disease targeted items (Burden of kidney disease) were presented as prespecified. In addition, the remaining seven multi-item scales were presented. Then, a generic preference-based measure of HRQoL was obtained using the EuroQol five-dimension descriptive system (EQ-5D-5L) (29). The EQ-5D-5L comprises five dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. The EQ-VAS was also obtained, whereby participants reported their self-rated evaluation of their health state on a 0 to 100 visual analogue scale. Costs of delivering the PEDAL intervention were calculated including exercise equipment, assumed to cost £1000 with a lifetime of 10 years and maintenance costs of £50 per year. Staff costs were assumed to include one x 0.6 full time equivalent physiotherapy assistant (mid band 4 Agenda for Change (AFC) scale, annual employer costs from £25866 outside London to £34787 in London) per 12 to 20 participants (to reflect

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different geographical spacing of kidney units in rural and urban areas) and one x 1.0 full time equivalent supervisor (mid band 8 AFC, annual employer costs from £55078.00 outside London to £71418.96 in London) per 80 participants.

Physical Function

Upper limits of exercise tolerance was assessed by peak oxygen uptake (VO_2 peak) determined by an incremental cycling protocol (26). Physical function limitations were assessed by the sit-to-stand-60 (STS60) (30) and gait speed over 10m (31). Physical activity behaviours were captured by the International Physical Activity Questionnaire Short Form (IPAQ-SF) (32); ability to undertake activities of daily living (ADLs) was recorded by the Duke Activity Status Index (DASI) (33); and fear of falling was assessed by the Tinetti Falls Efficacy Scale (TFES) (34).

Cardiovascular risk and clinical measures

Arterial stiffness was assessed by carotid-femoral pulse wave velocity (PWV) (35), using the Vicorder system (Skidmore Industries, UK) and following current recommendations (35). Measures of body mass index and waist circumference were also recorded. Clinical data including cause of kidney disease, comorbidities, routine clinical blood tests (hemoglobin (Hb), serum phosphate and parathyroid hormone), medications (including erythropoiesis-stimulating agents (ESAs)).

Harms

Harms were actively recorded in both groups by the physiotherapy assistants from baseline to the end of the six-month follow up period (n = 335). Relationship to the intervention was assessed by the lead clinician at each center, who was not blinded to treatment allocation.

Serious adverse events were reviewed by a data safety monitoring committee; rules for stopping the trial were that the committee identified a marked increase in expected or unexpected serious adverse events due to the testing or intervention procedures. Data on hospitalizations and deaths (all-cause mortality and cardiovascular mortality) were collected via reviews of clinical databases and records at each study visit.

Compliance and adherence (fidelity) to exercise prescription

General compliance was recorded as the percentage of exercise sessions completed out of the total prescribed for the six-month follow up period. Adherence (fidelity) was recorded as the percentage of patients who adhered exactly to the prescribed exercise (cycling and muscle conditioning exercises) at the prescribed intensity and cycling time duration for each session across the 6 months. In addition, the percentage of patients who temporarily (>2 weeks) paused exercise was noted. These data were recorded by physiotherapy assistants through completion of sessional exercise diaries.

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Statistical Analyses

The primary outcome measure (change from baseline to six months in KDQOL-SF 1.3 PCS) was compared between the control and intervention groups using a normal linear model adjusting for baseline KDQOL-SF 1.3 PCS and the randomization minimization variables (age, gender, diabetes status). The findings are presented as the adjusted mean difference {95% confidence interval} between the treatment groups. Significance was set at $p \leq 0.05$. The main analysis was carried out on research participants with PCS assessments at baseline and at six months. Two sensitivity analyses were also carried out, first imputing a score of zero for those who died prior to six months, and secondly based on all participants with a

baseline PCS using the method of multiple imputation. As results were consistent between methods, only the main analysis is reported herein.

Secondary continuous outcomes were analyzed as for the primary outcome. For health economic data, we estimated the mean between-group difference in costs of the intervention, and the mean between-group difference in quality-adjusted life years (QALYs) accrued by participants during the study, estimated as the area under the health utility curve from study entry (i.e. randomized and attended baseline visit) to follow up (six months later). Costs in the control group were set to 0. Estimated between-group differences in cost and QALYs were obtained by the method of recycled prediction in 5000 bootstrap samples. The distribution of these quantities was summarized and presented graphically in the incremental cost effectiveness plane. Time to event outcomes (cardiovascular and all-cause mortality) were calculated as time from randomization and were compared between treatment groups using Cox proportional hazards regression models. The results are reported as the adjusted hazard ratio for intervention versus control {95% confidence interval}. Data involving counts of events (hospitalisations) were compared between treatment groups using negative binomial regression models adjusting for length of follow-up. The results are reported as the adjusted rate ratio {95% confidence interval}. Harms (serious adverse events) were tabulated by system organ class and body system using the Medical Dictionary for Regulatory Activities (MedDRA) Terminology (36). Recurrent events were counted separately. Compliance and adherence data were tabulated and presented visually.

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RESULTS

Patient flow, including recruitment to and retention in the trial, is detailed in Figure 1. Two thousand four hundred and nine patients were screened for eligibility. Four hundred and ten were not eligible per inclusion criteria, 660 patients declined to participate, and 990 patients were not eligible to participate due to competing trials in this same population within the UK. Three hundred and thirty-five participants attended a baseline study visit, 175 patients who were randomised to EX and 160 participants to CON. The primary outcome was known for 243 (73%) of participants who attended a baseline visit, 116 (66%) participants in the exercise group, and 127 (79%) participants in the usual care group. More patients withdrew from EX (40; 34.5%) compared to CON (15; 11.8%), due to participant decision, physician recommendation due to medical concerns, and transplantation. Apart from an increased number of smokers in the group of patients who withdrew from EX, no obvious differences in characteristics of the withdrawn and not withdrawn groups were present (see Table 1).

Effect of intradialytic exercise training on health-related quality of life

For the primary outcome, the mean difference in the change in PCS from baseline to six months between EX and CON was 2.4 {95% confidence interval: -0.1 to 4.8} AU and was not statistically significant ($p = 0.055$). Similarly, other measures of HRQoL (Energy/Fatigue, Burden of kidney disease, EQ-5D-5L and EQ-5D VAS: see Table 2; the remaining seven multi-item scales from the KDQOL-SF: see Supplementary Table 1) were all unchanged by the intervention.

Cost effectiveness

The mean (SD) of the area under the EQ-5D-5L curve was 0.665 (0.248) in the control group and 0.653 (0.269) in the intervention group. The mean difference between treatment and intervention group obtained using the method of recycled predictions was -0.012 {95% CI: -0.069 to 0.043}, suggesting no difference in quality of life between the intervention and control groups (see Figure 2 for an example analysis calculated using a low staff to patient ratio, outside London). No significant subgroup effects were found for age, sex or diabetes at baseline.

Costs from different sources under different scenarios for staff costs are shown in Table 3. Average total costs per patient over six months range from £232 (US$299) {95% CI: £204 to £259) to £424 (US$546) {95% CI: £374 to £474}, depending on location and staff to patient ratio. The main cost factor was the staff cost for delivering the exercise sessions.

Effect of intradialytic exercise training on secondary outcomes

Consistent with the lack of change in HRQoL, there were no statistically significant or absolute changes in physical function outcomes (Table 4), cardiovascular risk (arterial stiffness: Table 4), or clinical measures (routine clinical blood tests and medications: data not shown). Although mortality was not influenced by the intervention, the number of hospitalizations tended to be higher in the EX group (Table 5). This trend was driven by 11 patients in the EX group who were each hospitalized more than four times during the trial for reasons deemed unlikely to be related to the intervention (e.g. fistula issues); in contrast only two patients in the CON group were hospitalized more than four times.

Harms

There was no noticeable increase in Serious Adverse Events in the exercise group (see Table 6). There was one noticeable SAE: an individual with type 1 diabetes and autonomic neuropathy experienced severe episodes of symptomatic hypotension that were possibly exacerbated by the intervention. The participant was withdrawn.

Compliance and adherence (fidelity) to the exercise prescription

A median (IQR) of 47 (28 to 77) % of exercise training sessions prescribed were completed by participants in EX. Only 18% of patients adhered exactly to the prescribed exercise type, intensity and duration. Moreover, during the six-month observation period, only 42% of participants avoided temporary cessation of the exercise intervention (Table 7). Reasons reported were fatigue and intercurrent medical events.

DISCUSSION

The aim of the PEDAL Trial was to assess the clinical value of a six-month intradialytic exercise program on quality of life, compared to usual care, for patients receiving HD therapy. The PEDAL Trial was novel in that it was the first to evaluate intradialytic exercise as would most likely be implemented, should health service commissioners include exercise training as part of the service specification for in-center hemodialysis. Unfortunately, as delivered, the PEDAL program did not statistically improve HRQoL, as assessed by the Kidney Disease Quality of Life Short Form Physical Component Summary (KDQOL-SF 1.3 PCS, $p = 0.055$); nor did it statistically improve quality of life as assessed by the prespecified secondary outcomes of EQ-5D-5L, EQ-5D VAS, or the KDQOL-SF 1.3 multi-item scales of Energy/Fatigue and Burden of kidney disease (see Table 2).

The lack of statistical improvement in the PCS can be explained in part by the PEDAL participants having poor compliance (only 47% of prescribed exercise sessions were completed) and very poor adherence (only 18% of patients adhered to the prescribed progression of overaload in terms of type, intensity and duration of exercise) to the exercise intervention. By design, the PEDAL trial aimed to have inclusive inclusion criteria. Consequently, baseline peak aerobic capacity values of 12 ml/min/kg were considerably lower than typically reported in previous studies (about 18 ml/min/kg) (10, 12, 18). This observation, combined with extremely low scores in physical performance (sit to stand and gait speed tests), confirm that the PEDAL cohort consisted of participants with severely low functional capacity. Arguably this makes the PEDAL cohort more representative and its findings generalizable to the current HD population. However, perhaps including such participants prevented benefits of the exercise intervention being realized over the relatively short six-month intervention, and it is possible that some of these highly compromised participants may require a slower rate of overload progression and adaptation/adjustment periods to an aerobic intradialytic exercise intervention. Poor compliance and adherence to implemented renal exercise programs in clinical practice is well documented, with more than 50% of the patients starting exercise reportedly dropping out by six months, often due to fatigue and being unwell (18, 37, 38).

That the PEDAL program was not effective to increase PCS warrants comparison to previous studies. A Cochrane review completed in 2011 concluded exercise was beneficial for HRQoL in patients with CKD, but unfortunately no meta-analysis or risk of bias assessment was performed, and many of the included studies were not representative of the hemodialysis population (9). Other reviews have concluded positive effects of exercise but not on PCS (16, 21, 38), or have relied on studies at high risk of bias and with considerable heterogeneity (17, 20). Previous meta-analyses have also included extra-dialytic exercise

programs (19, 39, 40), intradialytic exercise programs that were intensively supervised (e.g. (41)), or studies that have delivered progressive resistance training as opposed to aerobic cycling alone (10, 15, 42). In this regard, one meta-analysis (22) usefully compared aerobic vs. progressive resistance training vs. combined exercise; only progressive resistance training increased PCS. Detailed analysis of the very few empirical studies included in reviews that do show positive effects of aerobic intradialytic exercise on quality of life, reveals that they have often utilised interventions that would be difficult to implement in routine care (41). A recent study by Jeong et al (43) found no significant improvements in physical function or QOL with a combined oral protein supplement and intradialytic cycling programme. The authors suggested a more comprehensive lifestyle management approach would be required to elicit improvements in these parameters. Taken together with the results reported herein, it is highly unlikely that clinically implementable intradialytic aerobic exercise training alone can improve quality of life at a whole population level.

As well as assessing potential benefits, the PEDAL study uniquely assessed the cost of delivery of its intervention by recording harms and using health economic methods. The number of hospitalizations, all-cause mortality and cardiovascular mortality were not noticeably different between the groups. Although these results should be interpreted cautiously due to the low number of events, there was no increase in Serious Adverse Events (SAE) in the exercise group either. The economic cost of delivering the PEDAL intervention ranged from £464 (US$598) to £848 (US$1092) per participant per year (depending on pay band of the physiotherapy assistant, whether London weighting was applied and staff to patient ratio). Note this calculation assumed that physiotherapy assistants supervised between 6 and 10 participants per dialysis session without incurring any travel costs, and that exercise would be offered as part of a general physiotherapy service (with enough capacity to provide absence cover at no additional cost). It also assumes that patients will only exercise for

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between one and two sessions per week (the calculation is based on compliance to the PEDAL intervention, which was only 47%). For comparison purposes, the cost of delivering cardiac rehab is £477 (US$614) per person per year (44), equating to costs of £550 (US$709) to £12,558 (US$16,178) per quality-adjusted life year (QALY) gained (45). In contrast, PEDAL had no apparent quality of life gain, albeit over a relatively short period of observation of six months (cost effectiveness of rehabilitation programs increases with time (44, 45)). The cost of delivery of HD in the UK is approximately ~£35,000 (US$45,088) per patient per year (46). As the PEDAL Trial was not clinically effective at a whole sample level, whether the cost of delivery of intradialytic exercise is justified to enhance patient choice remains a matter for debate.

Limitations

PEDAL was designed to assess a pragmatic, clinically implementable intradialytic exercise intervention. By design, the study relied on a patient reported outcome measure for its primary outcome; it is recognized that the primary limitation of this study was the lack of an attention control group. In this regard, it is possible that an experimenter effect explains the 2.4 AU increase (albeit non-significant) in PCS (47). This interpretation is supported by the lack of absolute or statistical changes in objective measures of physical function, cardiovascular risk, and clinical measures (Table 2), consistent with a conclusion that intra-dialytic aerobic exercise *per se* had no clinical benefit. In addition, the study was not powered to detect differences in some secondary outcomes including mortality. Nevertheless, we reported these data to allow a balance of benefits and harms to be assessed. Future studies should address these concerns by including attention control arms and being adequately powered for all outcome measures. Perhaps the most important finding of the PEDAL study was the observation of poor compliance and adherence when intradialytic exercise was

implemented as part of routine care. It is acknowledged that the lack of absolute or significant change in objective measures may in part be due to limitations around effective implementation of delivering an adequate dose of exercise stimulus as indicated by the very low compliance and adherence data. PEDAL was designed to be a pragmatic intervention, no additional startegies to address low compliance or adherence were introduced. Thus future studies need to evaluate whether there are sub-groups of patients who may benefit from this type of intervention, and whether there is scope to optimize strategies to improve compliance and adherence with intradialytic cycling interventions, implementation settings and resources to deliver exercise-based interventions to improve effectiveness.

In conclusion, the PEDAL study was a rehabilitation program that could realistically be commissioned as part of routine care. Compliance and adherence with the exercise intervention, as per the study design, was extremely low. In this inclusive sample of people on hemodialysis, many of whom were severely deconditioned, the findings therefore suggest that six months of intradialytic aerobic exercise did not improve health-related quality of life.

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AUTHOR CONTRIBUTIONS

SAG, PK, JHM, ICM, IF, AS and TM conceived and designed the study; IF and CMM analyzed the data; SAG, JHM and PK interpreted, contextualized the data and drafted the paper; SAG, JHM, PK, DW, SB, KF, MT, PAK, MK, JB, ICM, IF, CMM, IDG, CR, MY, PT, TM, AS revised the paper; all authors approved the final manuscript.

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DISCLOSURES

The authors declare that they have no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Response of quality of life to the PEDAL intervention, as assessed by the Kidney Disease Quality of Life Short Form (KDQOL-SF 1.3) multi-item scales.

Consort checklist

Supplemental material can be found on the KI Reports web site.

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Table 1. Baseline characteristics of all patients in the trial, stratified by group, and according to withdrawal from the trial

		CON, not withdrawn		EX, not withdrawn		CON, withdrawn		EX, withdrawn	
		N	Summary	N	Summary	N	Summary	N	Summary
Age	Mean (SD) Median (Q1, Q3)	145	59.8 (14.1) 59.7 (50.5, 71.0)	135	60.5 (15.0) 62.1 (47.9, 72.9)	15	52.8 (19.9) 56.1 (34.7, 61.2)	40	56.8 (13.3) 56.3 (49.6, 64.3)
Gender	N (%) Female	145	55 (38%)	135	56 (42%)	15	4 (27%)	40	11 (28%)
Ethnicity	N (%) White N (%) Black Caribbean N (%) Black African N (%) South Asian N (%) Chinese N (%) Other	145	67 (46%) 26 (18%) 33 (23%) 15 (10%) 1 (1%) 3 (2%)	135	73 (54%) 17 (13%) 24 (18%) 16 (129%) 1 (1%) 4 (3%)	15	10 (67%) 1 (7%) 1 (7%) 2 (13%) 0 (0%) 1 (7%)	40	19 (48%) 3 (8%) 10 (25%) 6 (15%) 0 (0%) 2 (5%)
Weight (kg)	Mean (SD) Median (Q1, Q3)	143	80.8 (20.5) 77.0 (66.1, 92.2)	135	79.2 (18.8) 76.4 (65.4, 90.8)	15	82.5 (13.8) 83.0 (67.5, 91.5)	40	82.8 (24.8) 78.5 (67.4, 90.7)
BMI (kg/m^2)	Mean (SD) Median (Q1, Q3)	143	28.8 (6.5) 28.0 (24.5, 32.0)	135	28.5 (6.5) 27.0 (23.8, 32.2)	15	28.8 (5.5) 27.8 (24.2, 32.4)	40	29.2 (8.8) 27.6 (22.3, 32.6)
Smoking	N (%) Current N (%) Former N (%) Never	145	19 (13.1%) 45 (31.0%) 81 (55.9%)	135	18 (13.3%) 39 (28.9%) 78 (57.8%)	15	0 (0.0%) 4 (26.7%) 11 (73.3%)	40	5 (12.5%) 10 (25.0%) 25 (62.5%)
SBP (mmHg)	Mean (SD) Median (Q1, Q3)	142	138.6 (23.4) 138.0 (121.8, 153.9)	135	134.4 (21.3) 133.7 (121.3, 147.5)	15	133.9 (22.6) 130.0 (115.0, 152.2)	40	134.1 (17.5) 131.5 (121.0, 142.8)

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		CON, not withdrawn		EX, not withdrawn		CON, withdrawn		EX, withdrawn	
		N	Summary	N	Summary	N	Summary	N	Summary
DBP (mmHg)	Mean (SD) Median (Q1, Q3)	142	73.4 (13.7) 73.3 (63.2, 81.7)	135	72.6 (15.4) 71.3 (61.3, 82.7)	15	75.5 (15.4) 74.0 (67.0, 80.7)	40	76.9 (10.0) 76.8 (70.8, 81.5)
Peripheral vascular disease	N (%) Yes	145	6 (4.1%)	135	5 (3.7%)	15	0 (0.0%)	40	0 (0.0%)
Diabetes	N (%) Yes	145	59 (40.7%)	135	52 (38.5%)	15	6 (40.0%)	40	15 (37.5%)
Hypertension	N (%) Yes	145	116 (80.0%)	135	101 (74.8%)	15	11 (73.3%)	40	33 (82.5%)
Hyperlipidemia	N (%) Yes	145	39 (26.9%)	135	23 (17.0%)	15	4 (26.7%)	40	5 (12.5%)
Previous MI	N (%) Yes	145	21 (14.5%)	135	14 (10.4%)	15	0 (0.0%)	40	6 (15.0%)
Heart failure	N (%) Yes	145	17 (11.7%)	135	14 (10.4%)	15	0 (0.0%)	40	1 (2.5%)
Cerebrovascular events	N (%) Yes	145	17 (11.7%)	135	8 (5.9%)	15	1 (6.7%)	40	0 (0.0%)
Cardiovascular	N (%) Yes	145	25 (17.2%)	135	30 (22.2%)	15	2 (13.3%)	40	12 (30.0%)
Musculoskeletal and orthopedic condition	N (%) Yes	145	19 (13.1%)	135	16 (11.9%)	15	1 (6.7%)	40	7 (17.5%)
Hb	Mean (SD) Median (Q1, Q3)	141	110.2 (12.1) 109.0 (103.0, 119.0)	127	109.8 (14.1) 110.0 (102.0, 118.5)	15	118.1 (14.2) 115.0 (109.0, 124.0)	37	108.9 (15.8) 110.0 (100.0, 120.0)
CRP (mg/L)	Mean (SD) Median (Q1, Q3)	139	15.3 (21.1) 6.6 (3.1, 18.1)	125	11.9 (15.9) 6.0 (3.0, 14.1)	15	12.5 (16.4) 8.0 (4.5, 11.0)	36	21.1 (26.6) 10.9 (4.3, 28.1)
Dialysis efficiency (%)	Mean (SD) Median (Q1, Q3)	141	71.2 (8.4) 72.0 (66.0, 77.0)	125	71.9 (7.3) 73.0 (69.0, 76.5)	15	71.0 (11.3) 74.0 (68.0, 77.8)	37	71.6 (7.9) 71.8 (66.0, 77.0)

Continuous variables are shown as mean (SD) and median (Q1, Q3)

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Abbreviations: CON: control group; Ex: Exercise intervention group; BMI: body mass index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; Hb: Hemoglobin; CRP: C-Reactive Protein; URR: Urea Reduction Ratio. * Indian, Pakistani, Bangladeshi

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Table 2. Response of quality of life to the PEDAL intervention, as assessed by the Kidney Disease Quality of Life Short Form (KDQOL-SF 1.3) and EuroQol (EQ-5D-5L) questionnaires

		n[1]	Baseline	Month six	Adjusted mean difference in change between EX and CON groups[2]	p value[3]
Primary outcome						
KDQOL-SF 1.3 PCS (AU)	CON	120	32.9 (11.3)	31.8 (11.3)	2.4 {-0.1, 4.8}	0.06
	EX	114	33.8 (10.6)	34.8 (11.6)		
Secondary outcomes						
KDQOL-SF 1.3 Energy/Fatigue (AU)	CON	122	39.8 (26.0)	41.4 (24.9)	0.1 {-5.6, 5.8}	0.97
	EX	114	40.3 (27.2)	41.4 (26.4)		
KDQOL-SF 1.3 Burden of kidney disease (AU)	CON	122	36.0 (28.6)	37.3 (29.7)	-1.4 {-7.0, 4.1}	0.61
	EX	113	37.3 (27.7)	36.9 (29.0)		
EQ-5D-5L Health Utility Score (AU)	CON	121	0.69 (0.25)	0.68 (0.26)	0.01 {-0.04, 0.07}	0.69
	EX	111	0.71 (0.22)	0.70 (0.25)		
EQ-5D Visual Analogue Scale (0 to 100	CON	121	59.4 (22.7)	59.3 (20.9)	3.5 {-1.0, 8.1}	0.13

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scale)	EX	111	60.7 (22.2)	63.7 (19.3)

Data are mean (SD) or mean {95% confidence interval}. KDQOL, Kidney Disease Quality of Life Short Form (KDQOL-SF 1.3); PCS, Physical Component Summary; AU, arbitrary units; CON, control group (usual care maintenance hemodialysis); EX, exercise group (intradialytic exercise training plus usual care maintenance hemodialysis); EQ-5D, EuroQol five-dimension descriptive system. [1]number of participants with baseline and six-month data available; [2]adjusting for baseline data and the randomization minimization variables (age, gender, diabetes status); [3]comparison between the control and intervention groups using a normal linear model.

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Table 3. Costs per patient to deliver the PEDAL intervention over the six-month follow up period

Cost source	Outside London		London	
	Low staff:patient ratio	High staff:patient ratio	Low staff:patient ratio	High staff:patient ratio
Equipment purchasing and maintenance (£)	9 {8, 10}	9 {8, 10}	9 {8, 10}	9 {8, 10}
Staff delivering exercise sessions (£)	204 {180, 228}	341 {300, 381}	237 {209, 265}	395 {348, 441}
Training and oversight (£)	18 {16, 20}	18 {16, 20}	20 {18, 23}	20 {18, 23}
Total cost per patient over six months (£)	232 {204, 259}	368 {324, 412}	266 {235, 298}	424 {374, 474}
Estimated difference in cost (recycled predictions) (£)	234 {209, 260}	372 {331, 414}	269 {240, 299}	428 {380, 476}

Data are mean {95% confidence interval}. Estimated differences in cost obtained by the method of recycled prediction in 5000 bootstrap samples, setting cost in the control group to 0, adjusted for age, sex and diabetes at baseline.

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Table 4. Response of secondary outcome measures to the PEDAL intervention

		n[1]	Baseline	Month six	Adjusted mean difference in change between EX and CON groups[2]	p value[3]
Peak aerobic capacity (VO_2 peak, L/min)	CON	68	0.97 (0.38)	0.96 (0.37)	0.05 {-0.03, 0.12}	0.22
	EX	75	0.95 (0.42)	0.98 (0.43)		
Peak aerobic capacity (VO_2 peak, mL/min/kg)	CON	68	11.9 (4.5)	11.8 (4.2)	0.75 {-0.20, 1.71}	0.12
	EX	74	11.8 (5.3)	12.4 (5.7)		
Arterial stiffness by pulse wave velocity (msec) (22)	CON	78	8.10 (6.78, 9.29)	7.78 (6.97, 9.13)	1.01 {0.97, 1.06}	0.54
	EX	78	7.92 (6.62, 9.09)	7.88 (6.98, 9.27)		
DASI (AU)	CON	121	23.1 (13.1)	22.7 (13.4)	0.35 {-2.23, 2.93}	0.79
	EX	112	24.9 (13.3)	24.1 (14.3)		
IPAQ total physical activity (MET-minutes/week) [ln(x + 10)]	CON	118	423.8 (39.0, 1465.4)	353.2 (46.1, 1033.1)	1.36 {0.84, 2.21}	0.21
	EX	106	709.5 (153.8, 2515.1)	591.0 (111.8, 1793.2)		
Gait speed over 10m (m/s)	CON	84	0.86 (0.30)	0.87 (0.29)	0.01 {-0.04, 0.06}	0.73
	EX	79	0.94 (0.29)	0.94 (0.30)		
Sit to stand 60s (no. of repetitions)	CON	87	13.8 (6.6)	14.4 (7.0)	1.02 {-0.42, 2.47}	0.16

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	EX	82	15.8 (7.1)	17.1 (8.1)		
Tinetti Falls Efficacy Scale (AU)	CON	122	22.5 (10.2, 46.8)	24.5 (11.0, 50.0)	0.94 {0.80, 1.12}	0.49
[ln(x)]	EX	112	23.0 (11.8, 49.2)	24.5 (11.0, 46.2)		

Data are mean (standard deviation), median (IQR), or mean {95% confidence interval}; some variables were transformed to enhance model fit: transformations are given in [brackets]. CON, control group (usual care maintenance hemodialysis); EX, exercise group (intradialytic exercise training plus usual care maintenance hemodialysis); DASI, Duke Activity Status Index; AU, arbitrary units; IPAQ, International Physical Activity Questionnaire. [1]number of participants with baseline and six-month data available; [2]adjusting for baseline data and the randomization minimization variables (age, gender, diabetes status): note variables analyzed as log-transformed values are given as ratios; [3]comparison between the control and intervention groups using a normal linear model.

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Table 5. Numbers of hospitalizations and mortality during the PEDAL Trial

		n[1]	Number of hospitalizations (hospitalization rate per person year)	[2]Incident Rate Ratio {95% confidence interval}	p value[4]
Number of hospitalizations	CON	160	84 (0.54)	1.39 {0.93, 2.08}	0.109
	EX	175	132 (0.85)		
			Number of events (event rate per 100 person years)	[3]Hazard Ratio {95% confidence interval}	p value
All-cause mortality	CON	160	9 (5.8)	1.19 {0.48, 2.94}	0.71
	EX	174	10 (6.5)		
Cardiovascular mortality	CON	160	3 (1.9)	N/A	N/A
	EX	174	2 (1.3)		

CON, control group (usual care maintenance hemodialysis); EX, exercise group (intradialytic exercise training plus usual care maintenance hemodialysis); N/A, not applicable as numbers too small to analyze. [1]number of participants with baseline and six-month data available; [2]Incident rate ratios have been calculated in negative binomial regression predicting number of hospitalizations from treatment, adjusting for age, sex and diabetes at baseline. [3]Hazard ratios have been calculated in Cox Proportional Hazards regression models predicting survival from treatment. For all-cause mortality, survival was adjusted for age, sex and diabetes at baseline; for cardiovascular mortality, survival was adjusted for age and diabetes at baseline.

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Table 6. Number of patients with at least one SAE by MedDRA system organ class during the PEDAL Trial

	All	CON	EX
Number of randomized patients who attended baseline visit	335	160	175
Number of patients with any event	125	56 (35.0%)	69 (39.4%)
Blood and lymphatic system disorders	2 (0.6%)	0 (0.0%)	2 (1.1%)
Cardiac disorders	15 (4.5%)	6 (3.8%)	9 (5.1%)
Congenital, familial and genetic disorders	1 (0.3%)	1 (0.6%)	0 (0.0%)
Gastrointestinal disorders	14 (4.2%)	4 (2.5%)	10 (5.7%)
General disorders and administration site conditions	17 (5.1%)	12 (7.5%)	5 (2.9%)
Hepatobiliary disorders	3 (0.9%)	1 (0.6%)	2 (1.1%)
Infections and infestations	47 (14.0%)	18 (11.2%)	29 (16.6%)
Injury, poisoning and procedural complications	28 (8.4%)	12 (7.5%)	16 (9.1%)
Investigations	5 (1.5%)	4 (2.5%)	1 (0.6%)
Metabolism and nutrition disorders	17 (5.1%)	4 (2.5%)	13 (7.4%)
Musculoskeletal and connective tissue disorders	4 (1.2%)	1 (0.6%)	3 (1.7%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.3%)	0 (0.0%)	1 (0.6%)
Nervous system disorders	8 (2.4%)	3 (1.9%)	5 (2.9%)
Psychiatric disorders	4 (1.2%)	1 (0.6%)	3 (1.7%)
Renal and urinary disorders	1 (0.3%)	1 (0.6%)	0 (0.0%)
Reproductive system and breast disorders	2 (0.6%)	1 (0.6%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	13 (3.9%)	3 (1.9%)	10 (5.7%)
Skin and subcutaneous tissue disorders	1 (0.3%)	0 (0.0%)	1 (0.6%)
Social circumstances	1 (0.3%)	1 (0.6%)	0 (0.0%)
Surgical and medical procedures	37 (11.0%)	13 (8.1%)	24 (13.7%)
Vascular disorders	10 (3.0%)	6 (3.8%)	4 (2.3%)

CON, control group (usual care maintenance hemodialysis); EX, exercise group (intradialytic exercise training plus usual care maintenance hemodialysis).

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Table 7. Summary of exercise compliance and adherence to the PEDAL Trial intervention during the six-month follow up period

Compliance (percentage of expected sessions completed)	
Sample size *(n)*	175
Median (IQR)	47 (28 to 77)
Temporary (>2 weeks) cessation of exercise	
Sample size *(n)*	119
n (%)	69 (58%)
Adhered (fidelity to type/intensity/duration) to the exercise prescription	
Sample size *(n)*	119
n (%)	21 (18%)

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FIGURE LEGENDS

Figure 1. CONSORT diagram of the flow of patients across the various phases of the trial

Figure 2. Cost effectiveness: estimated differences in cost and QALYs on the ICER plane for a low staff:patient ratio, outside London (5000 bootstrap samples)

Figure 3. Number (%) of recorded incidents of temporary cessation (>2weeks) or missed exercise sessions with reasons

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Assessed for eligibility (N =

Excluded (*n*=2050)

- Did not meet inclusion criteria (*n*= 410)
- Declined to participate (*n*= 650)
- Other reasons eg: competing trials (*n*=990)

Enrollment

Randomly assigned (*n*= 379)

Did not attend baseline assessment (*n*=44)

- Died (*n*=3)
- Withdrawn (*n*=41)
  - Transplanted (*n*=8)
  - Participant decision (n=23)
  - Physician recommendation (*n*=7)
  - Adverse event (*n*=2)
  - Moved away (*n*=1)

Participants randomly assigned who attended baseline visit (*n*=335)

Allocation

Allocated to exercise intervention (n=175)

Allocated to normal routine care (n=160)

Withdrawal

Did not attend 6-month visit (n=59)

- Died (n = 3)
- Withdrawn (n=40)
  - Adverse event attributed to the intervention (n=1)
  - Adverse event not attributed to the intervention (n=5)
  - Participant decision (n=8)
  - Physician recommendation (n=9)
  - Moved away (n=1)
  - Transplanted (n=13)
  - Other (n=2: initiated PD; recruited to another study)
  - Unknown (n=1)
- Did not attend (n=16)
  - Missed visit (n=4)
  - Subsequently withdrawn due to participant decision (n=5)
  - Subsequently died (n=4)
  - Lost to follow up (n=3)

Did not attend 6-month visit (n=33)

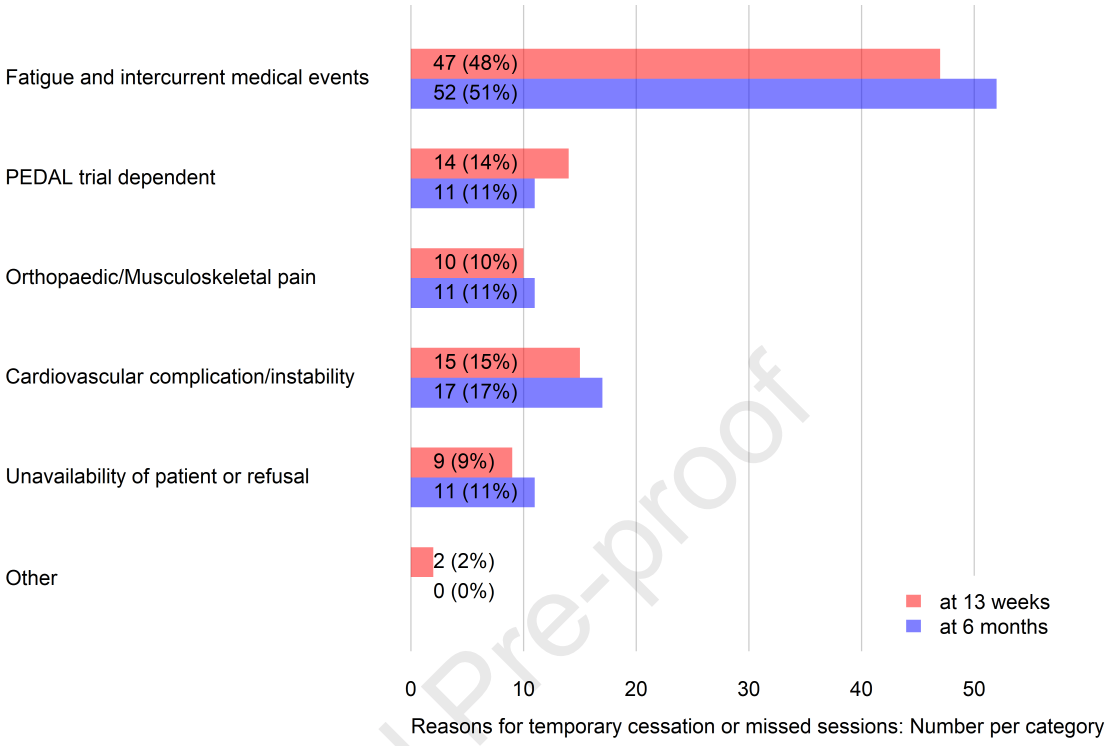
- Died (n = 4)
- Withdrawn (n=15)
  - Adverse event attributed to the intervention (N/A)
  - Adverse event not attributed to the intervention (n=1)
  - Participant decision (n=4)
  - Physician recommendation (n=1)
  - Moved away (n=2)
  - Transplanted (n=7)
  - Other (n=0)
  - Unknown (n=0)
- Did not attend (n=14)
  - Missed visit (n=7)
  - Subsequently withdrawn due to participant decision (n=7)
  - Subsequently died (n=0)
  - Lost to follow up (n=0)

Analysed (n=116)

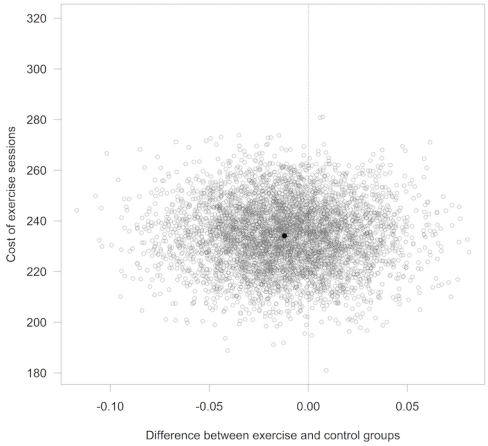
Analysis

Analysed (n=127)

Journal Pre-proof



Journal Pre-proof



Journal Pre-proof